REMARKS

Claims 65, 66, 68-144, and 146-157 remain pending in the application, claims 1-64, 67, and 145 having been canceled by a previous amendment.[1] Claims 94 and 98 have been rewritten as independent claims; claims 95-97 are amended to depend from claim 94, while claims 99 and 100 now depend from claim 98. None of these amendments alters the scope of the claims or adds new matter.

All of the claims were rejected on one or more grounds, as discussed below.

35 U.S.C. § 112, second paragraph

Claims 94-114 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. The Office action at page 2 states that claims 94-100 are drawn to a "suspension consisting of [a budesonide product] suspended in an aqueous solution," while claims 101-114 (which depend from claim 94) use open "comprising" language.[2] According to the Office action, "Because the claims use a combination of 'closed' (consisting of) and 'open' (comprising language, it is not clear what, if anything, is meant to be excluded." Applicants traverse.

Claim 94 (as amended) reads as follows:

> **A sterile, pharmaceutically acceptable suspension consisting of a micronized powder composition at least 98.5% by weight of which is pure budesonide or an ester, acetal or salt thereof, suspended in an aqueous solution.**

By virtue of the closed term "consisting of," claim 94 can contain only two components: (1) a micronized powder composition at least 98.5% by weight of which is pure budesonide or an ester, acetal or salt thereof, and (2) an aqueous solution. Note, however, that the language of claim 94 does not limit the constituents of the aqueous solution. The term "aqueous solution" implies that water is present, but it does not require that water be the sole ingredient in the solution. Claim 94 broadly permits the aqueous solution to contain unnamed ingredients dissolved in, and thus part of, the solution, so long as those unnamed ingredients are not

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[1] Applicants believe the omission of claim 146 from the lists of "pending" and "rejected" claims in the Office Action Summary at page 1 of the Office action was a typographical error.

[2] Note for the record that claims 101, 110, and 111 do not use the term "comprising."

inconsistent with other limitations of the claim (e.g., they must not render the product unsterile or pharmaceutically unacceptable). Claim 101 depends from claim 94, further specifying that one or more ingredients (such as a surfactant, pH regulating agent, etc.) from a specified list must be dissolved in the aqueous solution. Claim 101 therefore clearly further limits the scope of claim 94. Claim 102 depends from claim 101 and requires that the suspension contains a surfactant of a specified type, dissolved in the aqueous solution. Claim 102 therefore further limits both claims 101 and 94, again by describing a required constituent of the "aqueous solution." None of these claims uses closed language to describe the components of the aqueous solution; claim 102 actually uses the open term "comprising" to make it clear that, though a surfactant must be present in the aqueous solution, other (unnamed) components may also be present in the aqueous solution. The term "comprising" does not somehow override or conflict with the "consisting of" in claim 94 because the latter did not purport to limit the constituents of the aqueous solution. The "consisting of" in claim 94 does limit the scope of claim 94 and all claims that depend from claim 94 in that it excludes from the claimed suspension anything other than (1) a micronized powder composition at least 98.5% by weight of which is pure budesonide or an ester, acetal or salt thereof; and (2) an aqueous solution. It thus excludes, say, insoluble particles other than the specified budesonide powder composition, as well as solvents that are not miscible in the aqueous solution. It does not exclude substances dissolved in, and thus part of, the aqueous solution.

35 U.S.C. § 103(a)

Claims 65, 66, 68-83, 94-97, 101-109, 112, 115-117, 124-126, 130-132, and 139-141 were rejected as obvious over Harris et al. (US 6,187,765: "Harris") in view of Jakupovic et al (WO 96/32095; "Jakupovic"). According to the Office action, Harris teaches the filter-sterilization of a mometasone furoate (MF) solution, followed by precipitating the drug with water to produce particles, and "draws equivalence between MF and other glucocorticosteroids, such as budesonide and beclomethasone." Jakupovic is cited as teaching precipitation of budesonide from an organic solution. The Office action states that it would have been obvious to

prepare a sterile suspension comprising micronized budesonide, using the filter sterilization method of Harris. The rejection thus rests primarily on the teachings of Harris.

Applicants do not agree that Harris teaches an equivalence of MF and budesonide for purposes of suggesting a method of filter-sterilizing the latter. Furthermore, Harris does not even establish that one can reasonably expect filter sterilization to be a viable means of sterilizing MF, much less budesonide. However, the issue is moot, because (as explained below) Harris is not citable as prior art against the present claims.

The present application is a continuation of USSN 09/230,781 (now US Patent No. 6,392,036), filed January 29, 1999, which is the US national phase of PCT/SE98/02039, filed November 11, 1998, which claims priority back to a Swedish priority application (9704186-7) filed November 14, 1997. The claims are thus entitled to a **November 14, 1997** Swedish priority date and a **November 11, 1998**, US priority date.

Harris is not citable under 35 USC § 102(a) or (b). Harris published on the date it issued: February 13, 2001, which is long after applicants' earliest US priority date. Nor is Harris citable under 35 USC § 102(e). Harris was filed on October 6, 1998, claiming priority to a provisional application filed October 9, 1997. Attached hereto is a Declaration under 37 C.F.R. § 1.131, signed by all of the co-inventors of the present application, establishing that applicants had reduced their invention to practice in Sweden before October 9, 1997. Sweden has been a WTO member country since before January 1, 1996, and the date of invention sought to be established by this Declaration is not prior to January 1, 1996. This means that Harris is not "a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent," as required by § 102(e), and thus does not qualify as prior art under § 102(e).

As Harris has been removed as prior art, and the secondary reference, Jakupovic, does not teach anything about filter sterilization, the rejection of claims 65, 66, 68-83, 94-97, 101-109, 112, 115-117, 124-126, 130-132, and 139-141 as obvious over the combination of these two references must fail.

The Office action also cites Harris in combination with Jakupovic and four additional references (Guy et al. (US 5,540,930), Helzner et al. (WO 97/01341), Morice et al. (Clin. Pharmacol. Ther., 1996), or Jonsson et al. (Drug Metab. Dep., 1995), respectively) as rendering claims 110, 111, 113, 114, 118-123, 127-129, 133-138, 142-144, 148, 149, 152, and 153 obvious. (See the Office action at pages 5-7.) The additional references are cited for their alleged disclosures of details such as use of EDTA or thickeners, or use of the compositions in treating various conditions. Since Harris has been removed as prior art, these rejections also must fail. Withdrawal of all of these rejections based on Harris as the primary reference is respectfully requested.

Claims 84-93, 98-100, 146 and 147 were rejected as obvious over the disclosures of Jakupovic in view of Harris and Tainsh et al. (WO 95/31964; "Tainsh"). Claims 150, 151, and 154-157 were rejected over the same three references, further in view of Jonsson et al. (as cited above). Jakupovic is cited for its alleged teaching that respirable particles of budesonide can be produced by using water to precipitate the budesonide from an organic solution. According to the Office action at page 8,

> The reference does not teach a sterile product or the preparation of a suspension. In preparing this product under non-sterile conditions, it would inherently comprise viable microorganisms. Harris teaches that a suspension of budesonide is known and the importance of sterility for inhaled compositions.
>
> Tainsh teaches the preparation of a suspension comprising the glucocorticosteroid, fluticasone. The reference further teaches the sterilization of the prepared suspension using steam. See paragraph bridging pages 4 and 5.

The Office action concludes that it would have been obvious to prepare particles of budesonide as prepared by Jakupovic for use in a suspension as described by Harris and sterilize this suspension by steam as described by Tainsh for human administration. According to the Office action, "one of ordinary skill would reasonably expect success in using this sterilization process because it is taught for a sterilization of a suspension comprising a glucocorticosteroid." The fourth reference, Jonsson et al., is cited in combination with the other three for its alleged disclosure of the 22R epimer of budesonide (a limitation of claims 151, 155, and 157).

Although Harris has been removed as prior art (see above), applicants traverse the overall rejection of these claims not on that basis, but on two other grounds: (A) one of ordinary skill in the art would not have had a reasonable expectation of success in using steam to sterilize budesonide particles; and (B) steam sterilization would not produce the same product as dry heat sterilization. These grounds are elaborated below.

(A) One of ordinary skill in the art would not have had a reasonable expectation of success in using steam to sterilize budesonide particles.

(1) The requisite expectation of success cannot be found in Tainsh. The Examiner cites Tainsh for its disclosure that steam can be used to sterilize a fluticasone suspension. The cited disclosure is a single sentence at the bottom of page 4: "The bulk suspension is sterilized, conveniently by means of thermal sterilization using steam." This is the only mention of drug sterilization in Tainsh. There is no indication that Tainsh ever attempted to sterilize a fluticasone suspension—note, in fact, that Tainsh words it in the present rather than past tense, suggesting that the task had not been accomplished as yet. Tainsh provides no evidence that steam sterilization can be successfully carried out on a bulk suspension of fluticasone (or any other glucocorticosteroid) without altering the properties of the product. In view of other statements to the contrary in the art (discussed below), a bare assertion that a fluticasone propionate suspension can be sterilized using steam would be insufficient to convince one of ordinary skill in the art that there is a reasonable expectation of success in doing so. Tainsh does not even suggest that budesonide can be sterilized this way.

(2) The requisite expectation of success cannot be found in the other references cited by the Examiner. Jakupovic and Jonsson et al. do not mention sterilization. Harris states at col. 5, lines 45-55, with respect to the sterilization of the corticosteroid mometasone furoate monohydrate (MF):

> Alternative processes which may be considered for achieving sterility usually will not include sterilization steps for the micronized drug substance or formulation, since it has been found that the drug undergoes degradation under the influence of gamma-ray irradiation and sterilizing heat conditions.

Accordingly, Harris teaches away from use of "sterilizing heat conditions" to sterilize MF. The Examiner argued at page 3 of the Office action that Harris "clearly draws equivalence between MF and other glucocorticosteroids, such as budesonide and beclomethasone," which would suggest that the Examiner would read Harris as teaching away from using "sterilizing heat conditions" to sterilize not only MF, but also budesonide and other glucocorticosteroids.

(3) Those of skill in the art understood that moist heat treatment of corticosteroid particles would be likely to alter the size of the particles. Bernini et al., US 6,464,958 ("Bernini"; copy attached hereto as Appendix 1) describes a process for optimizing particle size of drug particles (particularly glucocorticosteroids including budesonide and fluticasone propionate—see col. 1, lines 19-21) in a suspension formulation, saying at col. 4, lines 7-13, that

> Said treatment might also be effective in restoring the desired particle size distribution after that unfavourable changes in their profile have occurred as a result of heat-sterilising processes. The latter methods may indeed lead to the formation of aggregates which will hardly de-aggregate into fine particles upon administration.

Although Bernini is not prior art to the present claims, it does provide a window into how the art was thinking in 1998 and suggests that the art would not have believed Tainsh's blithe statement that steam sterilization can be used, absent evidence to support it.

A later reference, McAffer et al., US 6,863,865 ("McAffer"; copy attached hereto as Appendix 2), also addresses sterilization of suspension formulations in general, and budesonide suspensions in particular:

> The sterilization of suspensions raises particular problems. The desired biological activity of the formulation commonly requires that the diameter of particles of the drug lies within a narrow range (typically less than 5 micrometers). The standard means of sterilization, that is the raising of the temperature of the formulation to 121° C. for 15 minutes, frequently destroys one or more of the components of the formulation. In addition this treatment results in the clumping or agglomeration of the drug particles in the suspension such that the efficacy of the resulting product is impaired or abolished.
>
> Known alternative methods for the sterilization of pharmaceuticals are inappropriate for sterilizing suspension formulations of drugs. Pharmaceuticals may be sterilized by passage [through] a filter having a pore size of not more than 0.2 micrometers. However this cannot be used in the case of many suspensions as the required particle size in these formulations is significantly greater than this filter pore size. Similarly, pharmaceuticals may generally be sterilized by gamma-irradiation, but

> budesonide, for example, is destroyed by such treatment. No further methods for the sterilization of pharmaceuticals are currently acceptable to regulatory agencies. (Col. 1, lines 24-45.)

McAffer puts it even more bluntly at col. 4, lines 48-49 (emphasis added): "**the sterilization of budesonide is generally considered by the market to be impossible.**" McAffer describes a purportedly novel method involving a "high temperature/short time" heat treatment and asserts that it allows sterilization of a budesonide suspension "**for which this was previously believed not to be possible**" (col. 4, lines 63-64; emphasis added). Thus, McAffer indicates (twice) that even in 2000 those of skill in the art still believed that sterilization of a budesonide suspension not only wasn't "obvious", in fact was "*impossible*." This is extraordinarily strong proof that the art at the time of the invention did not have a reasonable expectation one could successfully heat-sterilize a budesonide suspension.[3]

(4) Applicants tested steam heat treatment of a budesonide suspension, and found (consistent with the statements in Bernini and McAffer) that it alters the particle size in an unacceptable way. See the present application at page 3, lines 11-13: "moist heat sterilization, e.g., steam treatment of glass vials containing the product, leads to an unacceptable change in particle size."

Applicants have produced multiple lines of evidence that there would NOT have been a reasonable expectation in the art that steam sterilization of a budesonide suspension would yield a successful result. In fact, the bulk of the evidence is quite to the contrary. In the absence of a reasonable expectation of success in the art, the obviousness rejections cannot stand.

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[3] Note for the record McAffer's further statement beginning at col. 4, line 66, that "filter sterilization is not an absolute assurance of sterility as the integrity of the filter cannot be constantly monitored throughout the filling process." This indicates that the art also would not have considered use of filter sterilization to be an acceptable way to produce sterile budesonide, contradicting the Examiner's assertions to the contrary at page 4 of the Office action, in the discussion of Harris.

(B) Steam sterilization would not produce the same product as dry heat sterilization

The Office action states at page 8, "Although these claims [i.e., claims 84-93, 98-100, 146 and 147] are product-by-process, the burden is on Applicant to demonstrate a difference between the product prepared according to that described by the references and that prepared according [to] the invention." This is readily done.

All of claims 84-93, 98-100, and 146 specify that the claimed composition or suspension be "pharmaceutically acceptable." The method of steam-sterilizing a budesonide suspension that the Office action asserts is obvious would produce changes in the budesonide suspension that would render it no longer pharmaceutically acceptable, and so outside of these claims. This is evidenced, for example, by the teachings of McAffer quoted above and reiterated here for the Examiner's convenience:

> The sterilization of suspensions raises particular problems. The desired biological activity of the formulation commonly requires that the diameter of particles of the drug lies within a narrow range (typically less than 5 micrometers). The standard means of sterilization, that is the raising of the temperature of the formulation to 121° C. for 15 minutes, frequently destroys one or more of the components of the formulation. In addition this treatment results in the clumping or agglomeration of the drug particles in the suspension such that the efficacy of the resulting product is impaired or abolished. (col. 1, lines 24-34.)

Also as quoted above, Bernini points out at col. 4, lines 11-13, that heat sterilization of a suspension "may indeed lead to the formation of aggregates which will hardly de-aggregate into fine particles upon administration." Furthermore, the present application reports at page 3, lines 11-13, that steam heat sterilization of vials containing the suspension product leads to "unacceptable change in particle size." Since particle size is crucial to the effective administration of the inhaled suspension (see, e.g., Bernini at col. 1, lines 28-48), any process that increases agglomeration and/or particle size significantly will render the product no longer pharmaceutically acceptable, and thus outside the scope of the present claims.

Furthermore, Applicants point out that a number of the claims limit the sterilization process to a process that would not produce a composition obtainable by steam heat sterilization of an aqueous suspension. For example, claim 146 is explicitly drawn to a composition

"produced by dry-heat treatment of a viable-microorganism-containing powder," while claim 147 is drawn to a sterile powder composition prepared by heating a budesonide powder composition that contains viable microorganisms and less than about 1%(w/w) water (i.e., is substantially dry). By specifying conditions that exclude steam sterilization of an aqueous suspension, these claims ensure that there are at least two structural distinctions over the hypothetical steam-sterilized budesonide suspensions that the Examiner deems to be "obvious". First, the claimed compositions would not contain the aggregates (see above) that would plague steam-sterilized suspensions. Second, the claimed compositions would contain the detritus of dry-heat-killed microorganisms, a structural feature that would not be found in a steam-sterilized aqueous suspension. This conclusion is derived from the Ansel et al. (Pharmaceutical Dosage Forms and Drug Delivery Systems, 6th Edition, Williams & Wilkins, 1995; "Ansel") reference that is of record (see, e.g., the prior Office action dated November 1, 2005), which is instructive regarding the different results obtained with "moist heat" and "dry heat" sterilization. Ansel says at page 294, right column:

> The mechanism of microbial destruction in moist heat is thought to be by denaturation and coagulation of some of the organism's essential protein. It is the presence of the hot moisture within the microbial cell that permits destruction at relatively low temperature. Death by dry heat is thought to be by the dehydration of the microbial cell followed by a slow burning or oxidative process.

According to Ansel, a composition in which viable microorganisms were killed by dry heat would contain detritus of microbes that have been subjected to a "slow burning or oxidative process", in contrast to a composition in which the microorganisms were killed by "moist heat," resulting in dead microorganisms containing denatured and coagulated protein.

It is therefore clear that the compositions of at least claims 146 and 147 would not be identical to the steam-sterilized aqueous suspension composition that the Office action asserts is "obvious" in view of Jakupovic, Harris, and Tainsh.

Obviousness-type Double Patenting

Claims 65-70, 72-80, 84-117, 121-132, 136-144, 146 and 147 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of US 6,686,346 in view of Harris et al and Tainsh et al. According to the Office action at pages 9-10,

> Claims 1, 11, and 12[4] of '346 recite a suspension (or administration of said suspension) comprising budesonide suspended in an aqueous medium....Although it would be obvious to one of ordinary skill [to] prepare a suspension for inhalation in sterile form, Harris teaches this explicitly. Tainsh teaches steam sterilization of a suspension of a glucocorticosteroid.

The Office action at pages 10-11 sets forth an identical rejection of the same claims for obviousness-type double patenting over claims 1, 3, 7, and 8 of US 6,291,445 in view of Harris and Tainsh. Both rejections are traversed.

As discussed in detail above, it would not have been obvious to one of ordinary skill how one might produce a sterile, pharmaceutically acceptable budesonide composition that meets the criteria of the claims. Harris is not citable as prior art against the present claims, and anyway the post-filing date reference McAffer explains that filter sterilization (the method described in Harris) is not reliable (see the carryover sentence of columns 4-5). Both McAffer and another post-filing date reference, Bernini, point out that heat sterilization of a budesonide suspension leads to formation of aggregates, and applicants' own specification teaches that it produces changes in particle size. McAffer goes so far as to say at col. 4, lines 48-49, that "the sterilization of budesonide is generally considered by the market to be impossible." Regardless of how desirable a sterilized budesonide composition might have been, no one except applicants knew how to produce it at the present application's priority date. Applicants respectfully request withdrawal of all of the obviousness-type double patenting rejections.

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[4] Claims 1, 11, and 12 of the '346 patent are cited in this quoted text, though in the preceding sentence of the Office action, the rejection is formulated as being over only claim 1 of '346. The significance of this discrepancy is unclear. As the grounds for traversal apply in either case, applicants believe it is of no import.

Applicants submit that the present claims are in condition for allowance, and such action is requested. The Examiner is invited to telephone the undersigned if that will help expedite allowance.

Submitted herewith is a Petition for Extension of Time. Please apply the fee therefore, plus any other charges or credits, to deposit account 06-1050.

Respectfully submitted,

Date: November 1, 2007

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